REMARKS

Claims 1, 2, 4-12, and 14 are pending in the application. Claims 1, 2, 11, and 12 have been amended. Claims 5, 6, and 13 have been canceled. Support for the amendments can be found throughout the specification as originally filed. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the invention to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

In light of the claim amendments and the following remarks, Applicant respectfully request that the Examiner withdraw the rejections and pass this case to issuance.

Priority

The Examiner states that application serial nos. 60/116,748, 60/127,142 and parent application no. 09/491,896 fail to provide an enabling disclosure for the invention claimed in claims 1, 2, 4-12 and 14 for the reasons discussed under the rejection under 35 U.S.C. § 112, first paragraph. Applicants disagree with this assessment, and believe that the priority documents do provide adequate support. The claim amendments provided herewith and the remarks below address the rejections under 35 U.S.C. § 112, first paragraph. Accordingly, applicants request that the Examiner withdraw the objection to the priority claims.

Claim Objections

Claims 2, 5, 6, and 10 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claims. Applicants have canceled claims 5 and 6, and have amended claim 1. As amended, Applicants believe that claims 2 and 10 are not identical in scope to claim 1, and request reconsideration.

Claims 1, 2, 4-12, and 14 are objected to for reciting the phrase "a pharmaceutical acceptable carrier." As suggested by the Examiner, applicants have amended claims 1, 11, and 12 to recite "a pharmaceutically-acceptable carrier." Accordingly, the Examiner is respectfully requested to withdraw this objection.

Double Patenting

The Examiner states that "should Claim 12 be found allowable, Claim 11 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof." Applicants have amended both claims 11 and 12, and believe that these two claims are not substantial duplicates of each other.

Objections to the Drawings

The Examiner objects to Figure 4A for not being numbered consecutively. In response, Applicants have renumbered Figure 4A as Figure 4. Applicants have also amended the specification to reflect this change. Accordingly, Applicant respectfully requests that the Examiner withdraw the objections to the drawings.

Objections to the Specification

The disclosure is objected to because page 67 refers to images that are pseudocolored, but the drawings are in black and white. Accordingly, the specification has been amended to correct this issue. Applicant respectfully requests that the Examiner withdraw this objection.

Rejection of Claims 1, 2, 4-12, and 14 Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 2, 4-12, and 14 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for a composition comprising any vector encoding any NMDA receptor antigen, nor for a method of modulating or delaying onset of epilepsy, stroke, or decreased cognition in any subject, by administration of any vector encoding any NMDA receptor antigen." Applicant respectfully traverses this rejection.

While Applicant disagrees with the rejection, the claims have been amended to expedite prosecution. As amended, independent claim 1 recites a "a vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor antigen operably linked to a

promoter and capable of being expressed in a subject to elicit production of antibodies, and a pharmaceutically-acceptable carrier."

Amended claim 11 recites a "method comprising the step of administering a vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor antigen operably linked to a promoter and capable of being expressed in a subject to elicit production of antibodies, and a pharmaceutically-acceptable carrier to a subject, whereby the produced antibodies are capable of passing across a blood-brain barrier into a central nervous system following a neuronal insult." Support for this amendment can be found throughout the application as originally filed, and specifically, at page 64, lines 1-5.

Applicants point out that "following a neuronal insult, the blood-brain barrier has increased permeability to serum antibodies, and transport and subsequent binding to the target protein can occur. This 'on demand' or selective delivery of the neuroprotective agent (the autoantibody) limited both spatially to the site of injury and to the precise timing of injury is advantageous feature of the invention." (See, page 64, lines 1-5). Applicants submit that the specification clearly teaches that neuronal insults can increase permeability of the blood-brain barrier:

> "Antibodies are produced which are immunoreactive to the antigen, for example, the NMDA receptor and can cross the blood brain barrier, although at very low levels other than during injury or due to a disease process or excessive neuronal activity. When the blood-brain-barrier is compromised, the transfer of the antibody into the brain increases significantly. ....
>
> It is established that antibodies pass the blood-brain barrier poorly (Pollack and Lund (1990) *Exp. Neurol* 108:114-121), however, the blood-brain barrier is compromised after insults to the brain, including trauma, seizures, stroke or infection, allowing penetration of plasma molecules, including antibodies, into brain parenchyma.
>
> While not required to provide a mechanism of action, the genetic vaccine of the invention may provide neuroprotective effects when the integrity of the blood-brain barrier is compromised (*e.g.*, due to insult or injury to the brain,

disease or excessive neuronal activity). The compromise in the blood-brain barrier enables a breach of the immune privilege of the brain and passage of antibodies to the targeted neurons resulting in the characteristic disease phenotype. Accordingly, the invention features a method of treating neurological disorders by vaccinating against selected brain antigens to induce a state of autoimmunity. An immune response to a brain self-antigen can be induced which, instead of having disease-inducing activity, has a therapeutic efficacy..." (See page 2, lines 21-24; and page 37, lines 16-29).

As amended, independent claim 12 recites a method "comprising: administering a composition to a subject comprising a vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor antigen, and a pharmaceutically-acceptable carrier, wherein the antigen elicits the production of antibodies in a circulatory system of the subject which bind to an NMDA receptor in the central nervous system to ameliorate or delay onset of epilepsy or stroke in the subject."

The Office Action asserts that the claims are not enabled because of the "unpredictability inherent to the art of DNA vaccination and ...that the specification fails to enable to full scope of the claims." Applicants believe that the claims as amended are enabled, as discussed above, and that one of ordinary skill in the art would recognize that the claimed invention is useful for the recited disorders, and s/he can "make and use" the claimed invention without any undue experimentation. There is no reason to believe that the claimed invention will not help treatment of the disclosed disorders, and *in vivo* or clinical data is not necessary for patentability analysis.

Applicants believe that the claim amendments obviate the Examiner's rejections, and therefore request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of Claims 11, 12, and 14 Under 35 U.S.C. §112 Second Paragraph

Claims 11, 12, and 14 have been rejected under 35 U.S.C. § 112, second paragraph as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Claims 11, 12 and 14 are rejected as being indefinite since they recite the term "decreased cognition." This rejection is moot in light of the claim amendments.

Claims 11 is rejected as being indefinite in its recitation of "modulating or delaying onset of epilepsy, stroke, or decreased cognition." This rejection is moot in light of the claim amendments.

Claims 12 and 14 are rejected as being indefinite in its recitation of "modulating or delaying onset of epilepsy, stroke, or decreased cognition" in the preamble and to "modify the function of an NMDA receptor" in the conclusion. This rejection is moot in light of the claim amendments.

In light of these amendments, the Examiner is hereby requested to withdraw the indefiniteness rejections.

Rejection of Claims 1, 2, 4-8, and 10 Under 35 U.S.C. §103(a)

Claims 1, 2, 4-8, and 10 have been rejected under 35 U.S.C. § 103(a), as being unpatentable over Lissin *et al.* (PNAS 95: 7097-7102 (1998)) in view of Kammescheidt et al. (1996). Claims 5-6 have been canceled. Applicant respectfully traverses this rejection.

Lissin et al. simply describes a reagent that can be used in *in vitro* cell cultures to determine localization to synapses. The reagent (NR1) was epitope-tagged at the amino terminus with a signal sequence followed by a hemagglutinin (HA) epitope tag. Accordingly, the vector differs from that of the claimed invention. There is no suggestion or even a reason to assume that the *HA tagged* NR1 described by Lissin et al. can be *expressed in vivo*. Furthermore, there is no teaching or suggestion in Lissin that *HA tagged* NR1 can "elicit production of antibodies."

The Examiner states that "Lissin provides the explicit motivation to express epitope-tagged NMDA receptors (HA-NR1) *in vivo* for studying the conditions under which these changes in receptors surface expression occur *in vivo*." Lissin merely states that "[a]dditional important issues for future work include elucidating the NMDAR-dependent signal transduction

cascade that is responsible for the decrease in the surface expression of AMPAR clusters at synapses and determining under what conditions these changes occur *in vivo."* The Lissin reference does not indicate the nature of these further experiments, or indicate how the *HA tagged* NR1 reagent can be used in these future *in vivo* experiments. Accordingly, a person skilled in the art with knowledge of Lissin would not be motivated to look to the Kammesheidt reference for a description of *in vivo* gene transfer into the rat hippocampus for use with Lissin's *HA tagged* NR1 reagent.

Furthermore, there is no indication that the *HA tagged* NR1 described by Lissin would be "capable of being expressed in a subject *to elicit production of antibodies*," as recited by claim 1, and claims dependent thereto.

There is no suggestion or teaching in the reference that would encourage one skilled in the art to use a reagent for therapeutic uses. Accordingly, the Examiner is respectfully requested to withdraw the obviousness rejections.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. The Examiner is urged to telephone the undersigned Attorney for Applicant in the event that such communication is deemed to expedite prosecution of this matter.

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Respectfully submitted,

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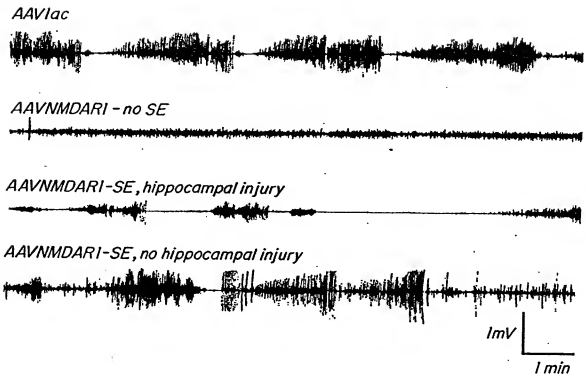
AAV1ac
AAVNMDAR1 - no SE
AAVNMDAR1-SE, hippocampal injury
AAVNMDAR1-SE, no hippocampal injury
1mV
1 min

FIG. 4A